microarray, and wherein said CNN circuit processes signals corresponding to the image of the DNA microarray by at least one of applying parameters associated with a cellular neural network and combining different processing results associated with chromatic components of the image of the DNA microarray.

46. (New) A method for analyzing an image of a DNA microarray, the method comprising:

acquiring at least one signal corresponding to the image of the DNA microarray, and

processing the at least one signal using a cellular neural network (CNN).

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47. (New) A method according to Claim 46 wherein the at least one signal comprises a plurality of signals, and wherein processing comprises processing the plurality of signals in parallel.

48. (New) A method according to Claim 46 wherein the image comprises a fluorescence image, and wherein processing the at least one signal comprises processing the plurality of signals associated with the fluorescence image.

49. (New) A method according to Claim 46 wherein processing comprises selectively processing a predetermined set of chromatic components of the image.

REMARKS

The specification has been amended to correct minor translation errors. Attached hereto under the caption **"Version with markings to show changes made"** is a marked-up version of the specification setting forth the changes made.

In addition, for better readability and the Examiner's convenience, the newly submitted claims differ from the earlier-amended, translated counterpart claims that are being canceled. The newly submitted claims do not represent changes or amendments that narrow the claim scope for any reason related to the statutory requirements for patentability.

It is believed that all of the claims are patentable over the prior art. Accordingly, after the Examiner completes a thorough examination and finds the claims patentable, a Notice of Allowance is respectfully requested in due course. Should the Examiner determine any minor informalities that need to be addressed, he is encouraged to contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The following heading has been inserted immediately preceding the sentence beginning at page 1, line 9:

-- Background of the Invention -

The following heading "Description of the prior art" at page 1, line 26 has been deleted.

Paragraph beginning at line 26 of page 2 has been amended as follows:

--In many DNA chips, the coupling of arrays of DNAis signalled by means of fluorescent materials. Notwithstanding, the procedure for [analysing] analyzing the chip, in particular to detect the levels of fluorescence, is rather costly.--

Paragraph beginning at line 17 of page 3 has been amended as follows:

--The method developed by Prof. Brown represents a first class of solutions. This method permits, by means of robot micro-machining, to chemically immobilize in 2 by 2 cm micro-grids fragments of cDNA (complementary DNA), or DNA reconstructed on the basis of RNA by reverse transcription. In this way, microarrays containing 10,000 individual cDNA elements are formed. The DNA fragment to be [analysed] analyzed is marked with fluorescent groups so to obtain different types of sensors to immediately distinguish the

fragments of DNA by means of the [colour] color of the corresponding fluorescent group with which they are treated. In this way, the microarray can be analyzed simultaneously during the hybridisation phase. The micro-grid is read by means of a confocal microscope at the end of the hybridisation phase providing a two-dimensional image in which [coloured] colored pins, or spots, appear arranged in a grid. The intensity of the various [colours] colors and their combinations is directly correlated to the intensity of the light output by fluorescence by the respective probes and to the degree of affinity between the probes and the individual genes deposited on the grid.--

Paragraph beginning at line 13 of page 5 has been amended as follows:

--Consequently, the idea of using a DNA chip has not been fully exploited to date, due to the difficulty in achieving real time analysis of the respective fluorescent images. Moreover, since diagnostic protocols generally require a certain number of microarray-based experiments, the time required for [analysing] analyzing the resulting images (processing times in the range of 10 to 30 minutes) abnormally hinder the efficacy of such method.--

The following heading "Object and summary of the invention" appearing at page 5, line 23, has been replaced with the following heading:

-- Summary of the Invention --

Paragraph beginning at line 33 of page 5 has been amended as follows:

-- [According to this invention, this object is attained thanks to a system having the characteristics which are specifically called for in the claims which follow.] This and other objects, features, and advantages in accordance with the present invention are provided by a system for automatically analyzing the images from a DNA chip after hybridisation. --

Paragraph beginning at line 1 of page 6 has been amended as follows:

--In essence, according to the currently preferred embodiment, the invention provides for making a system which [allows to automatically analyse] provides automatic analysis of the images from a DNA chip after hybridization. This is attained by acquiring the images [by means of] using optical matrix sensors and [by] processing the acquired images [by means of] using a Cellular Neural Network ([abbreviated to] CNN). Such a processing is essentially [analogue] analog and is achieved spatially on the entire development of the microarray matrix.--

Paragraph beginning at line 14 of page 6 has been amended as follows:

--According to the currently preferred embodiment of the invention, images are [analysed] analyzed by means of a

computing process which accounts for the physical-chemical rules at the basis of reactions on the microarray.--

Paragraph beginning at line 35 of page 6 has been amended as follows:

--More in particular, this invention relates to a system integrated in a monolithic fashion on a semiconductor for automatically [analysing] analyzing images, such as images from a microarray of the types comprising optical matrix sensors for the acquisition of images and to a high computing power parallel [analogue] analog processing architecture, based on the implementation of cellular neural network. Moreover, the invention [allows to integrate] provides integration of the entire image acquisition and processing system on a single chip.--

Paragraph beginning at line 15 of page 7 has been amended as follows:

--[In the enclosed drawings which are attached to this description:

- figure 1 illustrates a basic diagram of the embodiment of] FIG. 1 is a schematic view of a system for automatically analyzing images from a DNA chip after hybridisation[;] according to the present invention.

[- figures 2 to 5 illustrate, both in the form of block diagrams and in the form of charts, the criteria on which the organization and operation of the cellular network are based;] FIG. 2 is a schematic block diagram of a cellular neural network according to the present invention.

FIG. 3 is a more detailed schematic view of portions of a cellular neural network according to the present invention.

FIG. 4 is a schematic view of an electric circuit associated with the cellular network according to the present invention.

FIG. 5 is a plot of a weighted output value, h(x), as a function of an input signal, x, representative of the values used according to the present invention.

[- figure 6 illustrates an example of image] FIG. 6 is top plan view of a DNA chip after hybridisation and splitting thereof into three chromatic components as used according to the present invention[;].

[- figure 7 illustrates] FIG. 7 is a flow chart [which outlines the method whereby a cellular neural network image processing sequence is applied to each chromatic component of an image read from a DNA chip;] of a method of neural network image processing applied to chromatic components of an image read from a DNA chip according to the present invention.

[- figure 8 (which is split into two parts, identified by 8a and 8b, respectively) and figures from 9 to 12 illustrate, for example, the method according to which the] FIGS. 8a-12 illustrate various operations concerning filtering, segmenting, and the morphological operations, which can be implemented in a system according to this invention, can be conducted to isolate useful information with respect to the various sources of noise which could lead to false interpretations of the results during the automatic microarray image analysis process.--

The following heading "Detailed description

of a preferred embodiment of the invention" appearing at page 8, line 10, has been replaced with the following heading:

--Detailed Description of the Preferred Embodiments--

Paragraph beginning at line 12 of page 8 has been amended as follows:

--As mentioned above, the solution according to this invention offers an advantageous alternative with respect to traditional methods based on the analysis of fluorescence images generated by means of a DNA chip. In particular, the solution according to this invention [utilises] utilizes the class of arrays (generally two-dimensional) of [analogue] analog processors known as cellular neural networks (CNN) and implements a system which is able to process such images in real time.--

Paragraph beginning at line 30 of page 8 has been amended as follows:

--As further illustrated hereof, the system 20 can be configured as a cellular neural network (CNN) processing system, i.e. as an [analogue] analog, parallel processing system, preferably integrated in the same chip housing the block 10 in which the optical sensor is integrated.--

Paragraph beginning at line 1 of page 9 has been amended as follows:

--In particular (again with reference to the block diagram in figure 2), in addition to the array of [analogue] analog cells with optical sensors forming the block 10 in which the optical sensor is integrated, the system preferably comprises a set of [analogue] analog memories 11 which can co-operate with sensor 10, according to the criteria which are further described below, as well as an input/output circuit 12, which type is generally known.--

Paragraph beginning at line 13 of page 9 has been amended as follows:

--Preferably, the control logic 13 directly acts on the circuit 12. The same control logic 13 is usually configured so to directly operate on the array 10 by means of an [analogue/digital] analog/digital converter 14 to which the instructions contained in a program memory 16 selectively flow via a set of digital registers 15 for the configuration of the cellular neural network.

According to another important characteristic of the invention, the system 20 is configured as a cellular neural network which avoids the need to implement [analogue/digital] analog/digital conversion and/or vice versa of the values of each element or pixel in the image acquired at output of the optical sensor 10, also allowing to implement the microarray image analysis algorithm according to a totally parallel processing criterion. The various operations forming the algorithm are achieved by suitably setting the parameters which are programmed in the configuration registers 15 of the neural network on a case-by-case basis.--

Paragraph beginning at line 8 of page 10 has been amended as follows:

-- The circuit model of each cell 100 is shown in the diagram in figure 4, which schematically illustrates the values included in matrixes [A] A(ij;kl) and [B] B(ij;kl) and in the bias coefficient [I] Iij. [Said] The values [allow to] generate, from [a] an input signal, a corresponding output value which is [weighed] weighted by [means of] a function h(x) illustrated in figure 5.--

Paragraph beginning at line 18 of page 10 has been amended as follows:

--Returning to the block diagram in figure 2, the block 10 essentially consists of a matrix of [analogue] analog cells whose inputs are the signals corresponding to the optical sensors which read the image I generated in the microarray.

The [analogue] analog memory 11 is used to store the images and the intermediate processing stages. Conversely, the instructions and the respective parameters are stored in digital form in the memory 16 and in the registers 15 and are applied to the block 10 by means of the converter 14. The control logic 13 [synchronises] synchronizes the image acquisition and processing operations, in addition to the I/O signals to the end user which pass through the block 12.--

Paragraph beginning at line 21 of page 11 has been amended as follows:

--Obviously, the algorithms to be implemented depend on the type of analysis required by the expert. However, important steps, such as the reduction of the components, noise clearing, or the elimination of deformed spots, will need to be performed in any case. The example shows an algorithm which extracts from an image resulting from two red and green fluorescence probes the spots related to three different levels of each [colour] color indicating the three different degrees of affinity between the probes and the genes present in the micro-grid.--

Paragraph beginning at line 32 of page 11 has been amended as follows:

--Figure 6 illustrates an example of image I from a DNA chip after hybridisation. For classification of affinities, analyzing the two chromatic components R (red) and G (green) only will usually suffice. This is because there are no reactions able to generate appreciable levels of the component B (blue), i.e. the third component of the known RGB (Red Green Blue) [colour] color model.--

Paragraph beginning at line 15 of page 12 has been amended as follows:

--In the solution according to this invention, this form of pre-processing can be eliminated and simple [two-colour] two-color sensors, instead of Bayes sensors, can be used as sensors which are selectively sensitive to distinct chromatic components.—-

Paragraph beginning at line 20 of page 12 has been amended as follows:

--Furthermore, no [digitalisation] digitalization operation is required, since a typically [analogue] analog treatment is implemented. Consequently, applying an image processing sequence with cellular neural networks based on templates, for example according to the process outlined in the flow chart in figure 7, for each of the chromatic components (R and G) processed, will suffice.--

Paragraph beginning at line 29 of page 13 has been amended as follows:

--All the operations above, including the final logic AND operation, are carried out within the cellular neural network by means of templates, i.e. by means of suitable sets of parameters which are programmed in the network configuration registers (indicated by number 15 in the diagram in figure 2) on a case-by-case basis. The sequence of operations gives rise to a set of intermediate results corresponding to images which can be stored in the [analogue] analog memory of the system, indicated by number 11 in figure 2.--

Paragraph beginning at line 27 of page 16 has been amended as follows:

--The second advantage is the high processing speed which allows to process images which can also be large directly on-chip with very short processing times. Such times depend only on the value of the time constant RC of the cells

in the cellular neural network and the acquisition time of the optical sensors because no [analogue/digital] analog/digital conversion (and/or vice versa) is required for the values of each pixel of the image acquired at optical sensor output with respect to the processing matrix operating in parallel with implements the analysis algorithm of the microarray image.--

In re Patent Application of:
ARENA ET AL.
Serial No. **09/929,833**
Filed: **August 14, 2001**

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: DIRECTOR, U.S. PATENT AND TRADEMARK OFFICE, WASHINGTON, D.C. 20231, on this 1st day of ~~February~~ August, 2002.